Multinational Business Services, Inc.

Comments on the National Toxicology Program's Proposal to Change the Listing for 2,3,7,8-TCDD ("dioxin") to "Known to be a Human Carcinogen" in the Ninth Report on Carcinogens

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Before the Report on Carcinogens Subcommittee
of the NTP Board of Scientific Counselors
(supplemented by an oral presentation)

At NIEHS, Research Triangle Park, NC
October 31, 1997

1. **The listing decision is not a matter of scientific judgment only; it must conform to the listing criteria promulgated by the Secretary of HHS, which are "rules" legally binding on the NTP.**

The NTP carcinogen listing program is conducted pursuant to Federal statute *(1)*, and the Federal courts have held that the listing criteria are "rules", and that NTP listing actions are judicially reviewable *(2)*. Agencies must follow their own rules as law. If the agency is challenged for not adhering to the criteria, the courts will review a listing decision to see whether it is "not in accordance with law" under the Administrative Procedure Act *(3)*. In such a situation, where there is "law to apply", the standard of review is not simply whether the agency's action is "arbitrary and capricious", but also whether it is in accordance with law, including its own rules. In short, HHS and NTP must follow their own "rules" in the form of the listing criteria.

2. **The Draft Background Document *(4)* for the proposed listing change does not contain findings sufficient to satisfy the criteria for "known to be a human carcinogen".**

The criteria for the "known" category require that the Secretary determine that there is "sufficient evidence from studies in humans which indicates a causal relationship...." The Draft Background Document proposes to base the revised listing on a finding that "[h]uman studies have found an association" with cancers. There is no finding that the evidence is "sufficient" evidence of a "causal" relationship, as expressly required by the listing criteria. A "causal" association requires stronger evidence than a mere "association". Association and "strength" of association are simply one factor in evaluating whether the evidence is sufficient to infer a causal relationship. These are fundamental tenets of epidemiology. And, under NTP's listing criteria (as well as IARC's), "sufficient" evidence of a causal association must be differentiated from "limited" evidence, with the latter being sufficient only for category 2 listing ("Reasonably Anticipated") *(5)*.

3. **Under the NTP listing criteria, data on mechanism of action cannot compensate for lack of "sufficient" evidence" of a "causal relationship" "from studies in humans".**

There is nothing in the listing criteria for the "known" category that allows for mechanism of action data or other data to compensate for lack of "sufficient" epidemiologic evidence of a "causal relationship". When the dioxin listing nomination was originally reported in the press, it was reported that the nomination was based on the recent (Feb. 14, 1997) IARC reclassification of TCDD as "carcinogenic to humans". As noted at page 3-1 of the Draft Background Document, IARC found the human evidence to be "limited", but the Document goes on to imply that the overall evaluation and reclassification by IARC, of which the evaluation of human studies formed only one aspect, can be relied on for purposes

of the NTP proposed change in listing category. Such a position is not supportable. IARC found the human evidence to be "limited", and, as stated in the Seventh Annual Report on Carcinogens (the most recent Report), "the [NTP] Annual Report's . . . degrees of evidence are based on IARC's . . . degrees of evidence." *(6)*. While the NTP's degrees of evidence clearly correspond to IARC's (*e.g.*, the definitions of the terms "sufficient" and "limited" evidence), the NTP and IARC listing criteria incorporating the degrees of evidence, and on which the overall evaluations are based, are very different. In 1991, IARC revised its Group 1 category listing criteria to provide expressly that mechanism of action data could be used to compensate for human evidence that was less than sufficient in making its overall evaluation and determination of a listing category. The NTP criteria for its category 1, as revised (with non-substantive editing) in September 1996, do not so provide. The IARC Group 1 criteria state:

> This category ["carcinogenic to humans"] is used when there is *sufficient evidence* of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence in humans is less than sufficient but there is *sufficient evidence* of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity. [Italics as in original, indicating that the phrase is defined elsewhere in the Monographs Preamble.]

The NTP criteria for its "known" category do not provide for the use of mechanism of action data when there is "less than sufficient" human evidence; the NTP criteria require "sufficient" epidemiologic evidence of a causal relationship.

The Draft Background Document does not explain how its findings comport with the NTP listing criteria for "known". One can only speculate that the authors believe that the last paragraph in the statement of both sets of criteria, which follows the 2d category (beginning "Conclusions regarding...."), with its references to "all relevant data" and "data relating to mechanisms of action", somehow modify and change the explicit language in the criteria for category 1. Even though the version of the listing criteria contained at LC-1 in the Document are formatted in a manner that gives that impression, such an interpretation does not make sense in terms of plain English, and it would be contrary to the official version of the criteria approved by the Secretary, in which the last paragraph clearly refers only to category 2, not to both categories 1 and 2, and is formatted to reflect that position, not as in LC-1 *(7)*.

4. The evidence from human studies involving dioxin cannot reasonably be interpreted as "sufficient" evidence of a causal relationship.

Less than nine months ago, a 24-member Working Group convened by IARC, which was chaired by Dr. George Lucier of NIEHS and which included four other scientists from U.S. Federal agencies (NIEHS, NIOSH (2), and EPA), concluded that the human evidence

was "limited" rather than "sufficient". (At 342) NTP uses the same degrees of evidence. The IARC Working Group included at least eight voting expert epidemiologists. Despite finding that the human evidence was limited, the IARC Working Group voted to place TCDD in its Group 1 ("carcinogenic to humans"), relying on the portion of its Group 1 listing criteria (quoted above) that specifically allow mechanism of action data to compensate for less than sufficient human evidence *(8)*.

Contrary to what is stated in the Draft Background Document at RC-1, there is no significant new human evidence that was not considered by the IARC Working Group (and even if there were, the Document only says that it supports an "association", not a "causal relationship"). The Bertazzi manuscript that is currently "in press" and which is the only study cited in the Document for "additional findings [beyond IARC's]", and which is titled by the Document's authors as "A KEY HUMAN STUDY PAPER", is simply a slightly more elaborate version of the same risk findings presented in the Bertazzi et al. 1996 paper published in *Organohalogen Compounds*, and discussed and referenced in the IARC Monograph (see pp. 161-62, 531). Particularly for the cancer endpoints and risk measures relied on in the Draft Background Document (all cancers combined, non-Hodgkins lymphoma, and lung cancer), the number of observations and relative risks are the same between the 1996 and 1998 papers and are not significant (relative risks ranging from 0.6 to 1.2, or no data, in the various subcohorts) *(9)*. If anything, the Bertazzi et al. 1996 and 1998 papers detract from the weight of the evidence for the listing proposal *(10)*. Even the 1998 Bertazzi et al. manuscript Summary states that "the evidence in humans is limited", and that the data in the paper only indicate that "association [of certain cancer endpoints] with dioxin exposure is plausible", not that the findings indicate a causal relationship.

Another international panel of 19 experts, convened by the American Health Foundation with support from the National Cancer Institute, has also recently examined the evidence for human carcinogenicity of dioxin, with particular focus on its mechanism of action, and concluded (1996) that "[f]urther research is needed to determine whether the tumorigenic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rodents apply to humans." *(11)* This evaluation has not been referenced by NTP. In considering the apparent difference between the appraisal by this expert panel and that of IARC, with both considering mechanism of action, it might be noted that the IARC evaluation did not conclude, as required by its criteria, that there was "strong evidence in exposed humans that the agent (mixture) acts [in humans] through a relevant mechanism of carcinogenicity [found to cause cancer in animals]." Instead, IARC's overall evaluation (p. 343) concluded only that dioxin has caused cancer in experimental animals through a mechanism "involving the Ah receptor", and that the Ah receptor appears in, and functions similarly, in animals and humans. However, it is clear from the Monograph that binding to the Ah receptor is only an initiating biochemical event, not a mechanism of carcinogenesis, and that the full mechanism, and whether it operates similarly in humans and animals so as to be a common mechanism of carcinogenesis, is not known.

CONCLUSION: The proposed listing, in which NTP proposes to rely on non-human evidence to compensate for human evidence that is clearly not "sufficient" in order to list a substance in category 1, would be clearly contrary to the NTP listing criteria, and therefore contrary to Departmental policy and to law (and damaging to NTP's scientific credibility and reputation for objectivity). The proposal appear to be based to a large extent of the recent IARC re-classification of TCDD, but the IARC action does not support the proposal because the IARC listing criteria for Group 1 are very different from the NTP/HHS criteria, and IARC evaluated the human evidence as "limited" rather than "sufficient". The Subcommittee should recommend against the proposed listing change, and should recommend to both the NTP Executive Committee and the Director that the review process be terminated at the current Board Subcommittee level or that the NTP Executive Committee and the Director recommend against the listing. Additionally, the Subcommittee should recommend (1) that the presentation of NTP listing criteria currently included in the Draft Background Document (at LC-1) be revised to bring them into conformance with other controlling Departmental and NTP documents by making clear that the final paragraph pertains only to the "Reasonably Anticipated" category; and (2) that the statement at RC-1 regarding "Bertazzi et al., 1998 [in press]" be revised to make clear that the IARC Working Group considered the key risk findings contained in that manuscript, as reflected in Bertazzi et al. 1996, and that both Bertazzi et al. papers contain findings on all cancers combined, lung cancer, and non-Hodgkins lymphoma that are not consistent with the NTP proposal.

References and Notes

1. 42 U.S.C. 241(b)(4).
2. Synth. Organic Chem. Mfrs. Assoc. v. Secretary, DHHS, 720 F.Supp 1244 (W.D. La. 1989).
3. Id.; 5 U.S.C. 706, 702, 701(b)(2), 551(13).
4. We previously submitted comments on the proposed listing by letter to Dr. C. W. Jameson dated Aug. 22, 1997. At that time, there was no background document or other official NTP rationale for the dioxin listing nomination publicly available. The Draft Background Document before the Subcommittee was sent to us under cover dated Oct. 7, 1997. Since that Document is dated September 30, it apparently was not considered by the RG-2 committee, and we have no way of knowing what listing rationale was proposed to RG-2.
5. The reference at p. RC-1 to the IARC Working Group "noting" a "causal relationship" does not constitute a sufficient NTP finding, since IARC was simply noting that there was some evidence in support of a causal relationship, not that it was "sufficient" to indicate a causal relationship. IARC, after evaluating those studies, concluded in its overall evaluation that the evidence from studies in humans was "limited". Apparently the authors of the Draft Background Document recognize this point, since they proceed to state that the IARC notation of some evidence in support of a causal relationship "further strengthens the association", rather than stating that the IARC evaluation supports a conclusion that there is sufficient evidence to establish a causal relationship.
6. At 6.
7. In the *Federal Register* notice containing the 1996 revisions, signed by the Secretary, the

last paragraph clearly comes under the heading of "Revised BRC Criteria Reasonably Anticipated To Be Human Carcinogens". There is nothing in the notice under "Revised Criteria Known To Be Human Carcinogens" indicating any substantive changes, particularly regarding use of mechanism of action data or other data to compensate for human data that is less than "sufficient" evidence of a causal relationship; and, as stated in the notice, the only changes/additions are highlighted by underlining (converted to italics in the hard copy notice). 61 Fed.Reg. 50499 (Sept. 26, 1996) (both the hard-copy and GPO on-line versions). It seems obvious that if the Secretary's revisions were intended to make a substantive revision in category 1 along the lines implied by the Draft Background Document, such a revision would have been highlighted as a revision to category 1 in the notice. See also the HHS press release on the same date as the *Federal Register* notice, the news article in *Environmental Health Perspectives*, vol. 104, No. 8, p. 824, and the NTP "Update" for September 30, 1996. In other words, the presentation of the criteria in the Draft Background Document is not an accurate representation of the revised criteria as approved by the Secretary in 1996.

8. At 342-43, 631. The IARC Working Group's final plenary vote on the overall classification was a close majority vote of 14-10. Such a vote does not indicate convincing evidence, even if evidence other than evidence from human studies is given weight (which is not allowed by NTP category 1, but is allowed by IARC's Group 1).

9. The 1996 and 1998 papers can be seen to be essentially the same study by also comparing items such as the authors (three were inadvertently omitted by IARC in its endnote reference to the 1996 paper), the funding sources, the study period, and the endpoints evaluated. The Draft Background Document appears to acknowledge this in the last paragraph at 3-2, although the statement that the Seveso findings support the industrial cohort findings is clearly erroneous, since the Bertazzi et al. findings for all cancers combined, lung cancer, and non-Hodgkins lymphoma are inconsistent with the industrial cohort data in finding no increased risk.

10. This is reflected in the IARC Monograph at 191. IARC was of this opinion "because of inadequate duration of follow-up since the accident" -- *i.e.*, 15 years, 1976-1991 -- the same period examined in both the 1996 and 1998 Bertazzi et al. papers. And see note 9, above.

    The statements on p. RC-1 of the Draft Background Document regarding the four industrial cohorts show that the data from those cohorts were considered by IARC (Kogevinas et al., 1997, pp. 164, 570 of IARC Monograph), although the later statement in the Document regarding "additional findings [that] were not considered in the IARC evaluation" might seem to somehow encompass them. The only purported "additional findings" are in the yet-unpublished Bertazzi et al. manuscript. (It is odd that this "key" manuscript was not included in the Draft Background Document so it could be reviewed and commented on by members of the public who did not somehow have access to a copy.)

11. International Expert Panel on Carcinogen Risk Assessment, "The Use of Mechanistic Data in the Risk Assessments of Ten Chemicals: An Introduction to the Chemical Specific Reviews", *Pharmacol. Ther.* 71(1/20) (special issue titled "Cancer Mechanism and Risk Assessment"):1, 4. The International Expert Panel was comprised of Ames BN, Boyle P, Doull J, Corrado LG, Greim H, Hayashi Y, Hill RN, Kimbrough RD, Krewski D, Kroes, R, Monson RR, Munro IC, Rajewsky MF, Sheuplein RJ, Sugimura T, Swenberg JA, Travis CC, Whysner J, and Williams GM, with Sieber SM as Liaison from NCI.